# Next-generation ARIA care pathways for rhinitis and asthma : a model for multimorbid chronic diseases

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REVIEW

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# Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases

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## Abstract

**Background:** In all societies, the burden and cost of allergic and chronic respiratory diseases are increasing rapidly. Most economies are struggling to deliver modern health care effectively. There is a need to support the transformation of the health care system into integrated care with organizational health literacy.

**Main body:** As an example for chronic disease care, MASK (Mobile Airways Sentinel NetworK), a new project of the ARIA (Allergic Rhinitis and its Impact on Asthma) initiative, and POLLAR (Impact of Air POLLution on Asthma and Rhinitis, EIT Health), in collaboration with professional and patient organizations in the field of allergy and airway diseases, are proposing real-life ICPs centred around the patient with rhinitis, and using mHealth to monitor environmental exposure. Three aspects of care pathways are being developed: (i) Patient participation, health literacy and self-care through technology-assisted "patient activation", (ii) Implementation of care pathways by pharmacists and (iii) Next-generation guidelines assessing the recommendations of GRADE guidelines in rhinitis and asthma using real-world evidence (RWE) obtained through mobile technology. The EU and global political agendas are of great importance in supporting the digital transformation of health and care, and MASK has been recognized by DG Santé as a Good Practice in the field of digitally-enabled, integrated, person-centred care.

**Conclusion:** In 20 years, ARIA has considerably evolved from the first multimorbidity guideline in respiratory diseases to the digital transformation of health and care with a strong political involvement.

**Keywords:** Health care transformation, Care pathways, Rhinitis, ARIA, MASK, POLLAR

## Background

In all societies, the burden and cost of non-communicable diseases (NCDs) are increasing rapidly as advances in sanitation, public health measures and clinical care result in changes in demography [1]. Most, if not all, economies are struggling to deliver modern health care effectively [2]. Budgets will continue to be challenged with the move towards universal health coverage as demand increases and newer, more expensive technologies become available [3–5]. Traditional programmes, heavily reliant on specialist and supporting services, are becoming unaffordable. Innovative solutions are required to alleviate

system wide pressures [6, 7]. There is a need to support authorities in the transformation of the health care system into integrated care with organizational health literacy [8].

Integrated care pathways (ICPs) are structured multidisciplinary care plans detailing the key steps of patient care [9]. They promote the translation of guideline recommendations into local protocols and their application to clinical practice. They may be of particular interest in patients with multimorbidities since guidelines rarely consider them appropriately [10, 11]. An ICP forms all or part of the clinical record, documents the care given, and facilitates the evaluation of outcomes for continuous quality improvement [12]. ICPs should be carried out by a multidisciplinary team including physicians, pharmacists [13, 14] and allied health care professionals [15]. ICPs should integrate recommendations from clinical practice guidelines, but they usually (i) enhance recommendations by combining interventions, integrating quality assurance and (ii) describe co-ordination of care. Self-care and shared decision making are at the forefront of ICPs with the aim of empowering patients and their (professional and lay) care givers.

Rhinitis and asthma multimorbidity can be used as a model for chronic diseases since there is a broad agreement on the 'gold standard' of care [16–18]. In allergic rhinitis (AR) and asthma, adherence to treatment is a major unresolved problem [19, 20]. The vast majority of physicians prescribe regular treatment but patients (and physicians when they are allergic [21]) do not adhere to the advice. Instead of they self-treat based on personal experience as suggested by real-world data [19, 22]. There is thus a major disconnect between physicians and patients, either because of the clinical approach utilised or due to a lack of patient health literacy, with insufficient shared decision making (SDM). On-demand (prn) approaches are now proposed in both diseases [23–25] and represent a major change from previous recommendations. This new approach should be integrated in ICPs, but it needs to be applied to self-management and based on solid evidence.

ICPs have been proposed with a focus on new technologies that, through personally-held data on tablet devices and recording of 'symptom load', should enhance self-management and adherence to guidelines and ICPs. The science of supporting self-care and ICPs through mobile devices (mHealth) is in its infancy, but preliminary results are encouraging [26–28]. In the context of asthma, a systematic review showed that mobile apps were generally as effective as traditional models of supported self-management, but that they may be preferred in some clinical and demographic contexts as being convenient as well as efficient for the patient and the professional [29]. Standardisation and the establishment of the Privacy Code of Conduct for mHealth apps [25] will be important in ensuring patients on the safeguard of their data and in helping them choose reliable technological tools, which will be essential for ICP implementation.

As an example for chronic disease care, a new development of the ARIA initiative (ARIA phase 4) [30], along with POLLAR (Impact of Air POLLution on Asthma and Rhinitis), in collaboration with professional and patient organizations in the field of allergy and airway diseases, are proposing real-life ICPs centred around the patient with rhinitis, and using mHealth to monitor environmental exposure.

The current document was finalized and reviewed during a meeting involving ARIA, POLLAR (Impact of Air POLLution on Asthma and Rhinitis (EIT Health)), the European Innovation Partnership on Active and Healthy Ageing and the Global Alliance against Chronic Respiratory Diseases (GARD, WHO Alliance). Major allergy societies and patient's organizations participated in this meeting (Paris, December 3, 2018). The event was carried out with the support of many organizations (Fig. 1).

## The gaps in allergic rhinitis and asthma

AR is the most common chronic disease worldwide. Treatment guidelines have improved the knowledge on rhinitis and have had a significant impact on AR management. However, many patients still fail to achieve sufficient symptom control [31] and the costs for society are enormous, in particular due to a major impact on school and work productivity [32] and on allergic or non-allergic multimorbidities [33, 34]. Allergic Rhinitis and its Impact on Asthma (ARIA) has promoted the use of its recommendations [16, 35, 36] to be integrated in ICPs using mobile technology in AR and asthma multimorbidity across the life cycle [37].

The clinical problem is that a large number of AR patients do not consult physicians because they think their symptoms are 'normal' and/or trivial, even though AR negatively impacts social life, school and work productivity [36]. Many AR patients rely on over-the-counter (OTC) drugs and do not see the need to consult with physicians [38–41]. The vast majority of patients who visit general practitioners (GPs) or specialists have moderate-to-severe rhinitis [42–46]. ICPs should take this reality into account and consider a multi-disciplinary approach as proposed by AIRWAYS ICPs (Fig. 2).

## Supported self-management

People with AR and asthma are, by default, making day-to-day decisions about the management of their condition (avoiding triggers, using various treatments and seeking professional advice). Reflecting this broad concept, self-management is defined as "the tasks that individuals must


**Fig. 1** Organizations supporting the meeting

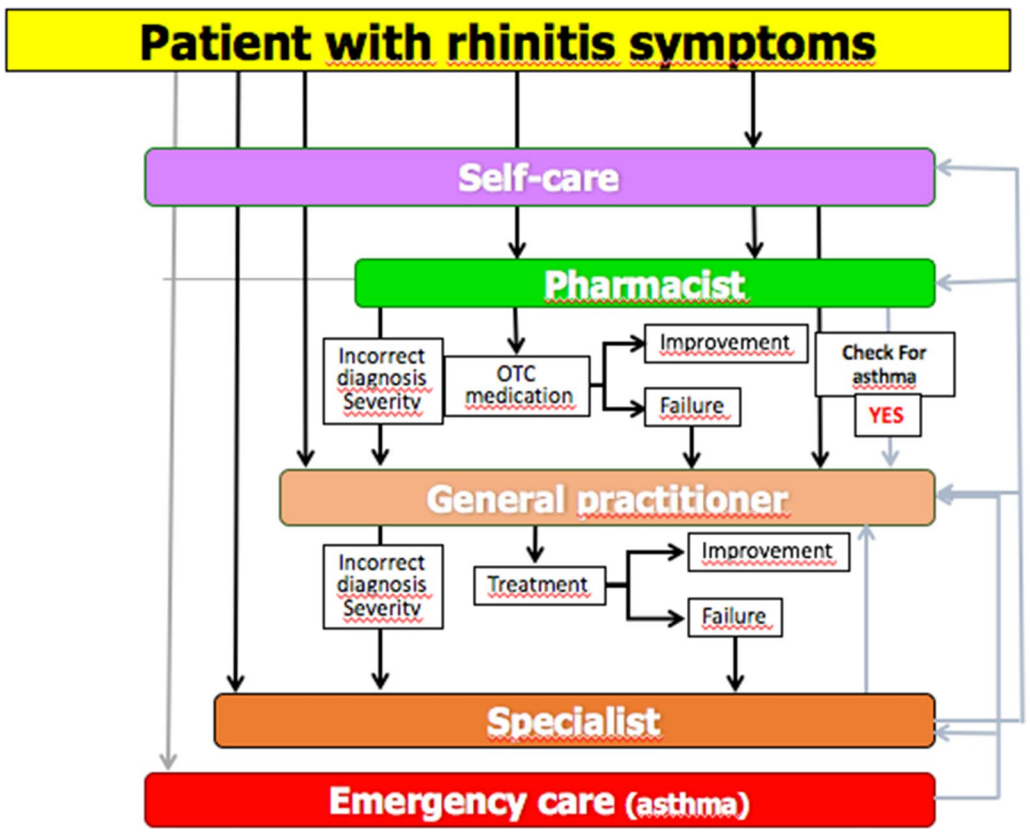


**Fig. 2** ICPs for rhinitis and asthma multimorbidity (adapted from [102])

undertake to live well with one or more chronic conditions. These tasks include having the confidence to deal with the medical management, role management and emotional management of their conditions" [47].

The term self-care includes generic "healthy lifestyle behaviours required for human development and functioning" [48]. However, self-care and self-management overlap as, for example, smoking cessation is a generic

self-care behaviour and a component of self-management for people with respiratory conditions.

Self-management support is the assistance that professionals (pharmacy, primary care, specialist), patient's organizations and other sources of information, as well as informal caregivers, give patients in order to make decisions about their condition and to manage disease and health-related tasks [49]. A taxonomy of 14 components of self-management support [50] offers a pick-list of activities that may be considered when planning self-management. These could be practical activities (e.g. teaching inhaler technique, discussing an action plan, helping to quit smoking) and imply SDM [50]. Mobile technology has the potential to contribute to many aspects of the supported self-management of chronic diseases [51].

Supported self-management is a 'key principle' for ICPs in long-term conditions [52, 53]. This not only reflects the paradigm shift towards SDM, but also includes pragmatic, economic imperatives, as healthcare systems respond to the increasing NCD burden. The economic impact of effective supported self-management goes beyond healthcare savings. For example, major economic return can be in the workplace where absenteeism and, more importantly, presenteeism are reduced [32] leading to an increased productivity.

Patient activation, defined as the "knowledge, skills and confidence a person has in managing his/her own health and health care" [54], is a goal of many ICP models. "Activation" encompasses the patients' beliefs about their ability to self-manage (self-efficacy) and the likelihood that they will put these beliefs into action. Levels of activation range from the disengaged patients who let others manage their condition to the fully "activated" patients who embrace SDM and manage their health in partnership with their healthcare advisors, understanding the escalation of treatment options and when to seek pharmacy or medical advice. Higher levels of activation have been associated with better process and health outcomes in adults [55] and there is some evidence that appropriately-targeted self-management support may be more beneficial to disadvantaged groups than to higher literacy/socioeconomic status patients.

Although ARIA appears to meet the patient's needs, real-life data obtained using the *Allergy Diary* (MASK-air®) app from around 10,000 people in 23 countries (Argentina, Austria, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Lithuania, Mexico, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, UK. Brazil is a developing country) have shown that very few patients are being treated according to guidelines and that they often self-medicate [19]. Self-medication is the treatment of common health problems with medicines without medical supervision. It is important to ensure that well-written, short and accurate self-management information is available for people to pick up in pharmacies, or for download. In the case of AR, many patients have prescribed medications at home and, when symptoms occur, they use them. Self-care and SDM centred around the patient should be used more often [56]. ARIA has already followed a change management (CM) strategy embedding the AR-asthma multimorbidity in every day practice [30], but a new CM is now being considered to increase the benefits of self-care and SDM in ICPs using currently-available IT tools. In the case of AR and asthma multimorbidity, aeroallergen exposure and pollution impact disease control and medications. However, there is currently no ICP in airway diseases that takes such environmental parameters into account [57]. These initiatives should prepare and support individuals, teams and organizations in making organizational change centred around the patient.

mHealth, such as apps running on consumer smart devices, is becoming increasingly popular and has the potential to profoundly affect health care and health outcomes [58]. Several apps exist for AR and asthma [59–63]. A review of the Apps in the field of allergic diseases has recently been completed (Matricardi et al. in preparation). One of the reviews—MASK (Mobile Airways Sentinel NetworK), the Phase 3 ARIA initiative [37, 64]—is based on the freely-available MASK app (*the Allergy Diary*, Android and iOS platforms) for AR and asthma. Importantly, MASK is available in 17 languages and deployed in 23 countries [64]. Data from 26,000 users reporting over 200,000 days of treatment are available. It complies with the recent General Data Protection Regulation (EU) 2016/679 (GDPR) enforced by the EU, May 25, 2018 [65]. The GDPR aims primarily to give control to citizens and residents over their personal data and to simplify the regulatory environment by unifying the regulation within the EU [66, 67]. Importantly, MASK enables the assessment of treatment patterns in real life and provides detailed information on treatment, given that the *Allergy Diary* is able to distinguish between AR medications [19].

## On-line information

Most patients check on-line to help them decide what the problem is and how to address it. This is a crucial self-management area of support and we need to think about how it can be optimized. Because of the multiplicity of sources and the lack of reliability control, it should be recognized that such a task would require an enormous effort. Consequently, it has been abandoned by many

other bodies/disease areas. One approach that may be of value in improving reliability would be to focus on sites that provide useful information and generate an accreditation process with international standing.

## Pharmacist care

Pharmacists are trusted health care professionals. Most patients with rhinitis are seen by pharmacists who are the initial point of contact of AR management in most countries. Depending on the country, few or most AR medications are available over-the-counter (OTC) [68–71] and are used by many patients. Therefore, as trusted health care professionals in the community, pharmacists are well placed to play a critical role identifying the symptoms of AR, recommending appropriate OTC treatment [38, 39, 41] and integrating health care teams through ICPs [13, 14]. The specific role of pharmacists in the management of AR within ICPs can been evidenced from several strategies that have been initiated [72] or completed and from studies confirming the important impact of pharmacist interventions on AR outcomes [40, 70, 73–80].

ARIA in the pharmacy 2004 [38] is being revised in order to propose ICPs involving a multi-disciplinary approach. This paper has been built on the evidence and provides tools intended to help pharmacists give optimal advice/interventions/strategies to patients with rhinitis. The ARIA-pharmacy ICP includes a diagnostic questionnaire specifically focusing attention on key symptoms and markers of the disease, a systematic Diagnosis Guide (including a differential diagnosis) and a simple flowchart proposing treatment for rhinitis and asthma multimorbidity. Key prompts for referral within the ICP are included. The use of technology is critical for enhancing the management of AR. The ARIA-pharmacy ICP should be adapted to local health care environments/situations as large regional or national differences in pharmacy-based care exist.

## Next-generation guidelines

Practice guidelines contain evidence-based statements about treatment, tests, public health actions and policy decisions intended to assist recipients of care and their care providers in making informed decisions.

ARIA was one of the first chronic respiratory disease guidelines to adopt the GRADE (Grading of Recommendation, Assessment, Development and Evaluation) approach, an advanced evidence evaluation and development approach for guidelines [16, 81–83]. GRADE-based guidelines are available for AR from other organizations and their recommendations are similar [16–18]. However, a limitation of GRADE is that evidence often lacks applicability because the populations studied do not reflect most of the patients seen in primary care [84]. The GRADE recommendations are often based on RCT in which patients regularly use their treatment, whereas most AR or asthma patients are non-adherent. GRADE rarely includes recommendations based on implementation research.

The more recently completed work by the GRADE working group on its Evidence to Decision Frameworks requires that guideline developers regularly address implementation and monitoring strategies [85–89]. Searching for and synthesizing evidence of effective implementation strategies enabled the BTS/SIGN asthma guideline to make a recommendation on how supported self-management for asthma could be embedded into routine practice [90]. Strategies include proactively engaging and empowering patients, training and motivating professionals as well as providing an environment that promotes self-management and monitors implementation [91]. In AR, cluster-randomized controlled trials have confirmed the overall value of guidelines [92, 93]. However, there has been only one direct testing of individual guideline recommendations in real–life studies in an effort to achieve optimization [94].

Next-generation ARIA-GRADE guidelines should consider testing the recommendations based on the GRADE approach with real-world evidence (RWE) using data obtained by mHealth tools such as MASK in order to confirm the efficiency or to refine current GRADE-based recommendations. The first results of MASK confirm the feasibility of the project [19]. Adherence to treatment is very low as < 5% of users record symptoms and medications for a period of 2 weeks. This indicates that it is important to further test whether on-demand is equally or even more efficient than regular-continuous treatment and that guidelines should consider both regular and on-demand treatment [19, 95].

Guideline recommendations often address isolated questions or focus on a single disease or problem. They should be considered in the context of the many decisions that are made. ICPs try to address the multiple options and iterative changes in a patient's status and problems. Guideline recommendations should support these iterative changes.

The key challenge for conventional treatment guidelines is that available evidence, both from randomized trials and non-randomized studies, does not usually address the complex pathways, but only affects isolated decision points within a pathway. For example, when an oral $H_1$-antihistamine is not achieving symptom control, we propose to replace it by an intra-nasal corticosteroid. However, this is often not the way that studies are designed and not how patients use these medications.

Assuming that properly developed pathways require evidence, our guidelines must start identifying the best available evidence to support decision points. When the evidence is indirect, which is frequently the case, connecting the relevant decision points and considering all of that evidence together results in low certainty on the overall structure and timing of an ICP.

The next-generation guidelines, if complemented by the intelligent use of tools such as MASK, which records patients' symptoms and provides advice at given time points to follow ICPs, could exemplify unique new tools to both implement and evaluate recommendations in the context of pathways. Studies should be carried out in which patients are randomized to ICPs or to follow ARIA recommendations that are not presented as pathways. Such studies will provide both information on the use of the recommendations and on the usefulness of the pathways. Through implementation of recommendations, we will be able to increase our certainty in the evidence by evaluating the entire pathway and measuring outcomes in direct population-based studies that record what patients do as opposed to what clinicians prescribe (and patients do not do).

## Study proposals of ARIA phase 4 and POLLAR

ARIA Phase 4 is the change management strategy for AR and asthma [96]. POLLAR is an EIT-Health (European Institute for Innovation and technology) project which aims to better understand, prevent and manage the impact of air pollution and allergen exposure on airway diseases [57]. POLLAR will use the MASK App, which is a Good Practice [64]. One of the POLLAR work-packages is the development of ICPs integrating aerobiology and air pollution. This will be developed using a stepwise approach centred around the patient. The four-step project is a WHO Global Alliance against Chronic Respiratory Diseases (GARD) demonstration project.

### Step 1: First meeting (December 3, 2018, Paris): Development of next-generation ICPs with a focus on self-management, pharmacy care and next-generation guidelines

The Paris meeting addressed a number of areas as delineated below (Fig. 3).

### Step 2: 2019–2021: Further development and implementation of next-generation ICPs

1. Develop a strategic and practical approach to improving patient autonomy and self-management programmes.
2. Deploy to other chronic respiratory diseases (asthma, COPD and rhinosinusitis [97]) and NCDs developing a multimorbidity App based on MASK expertise and experience.
3. Develop documents for specific age groups: preschool and school children, older adults.
4. Establish a best practice across several regions in the EU linking the study to policy makers aiming to improve air quality and outcomes in their population.

### Step 3: Second meeting (December 2019): Embedding environmental data in next-generation ICPs

Using the results obtained by POLLAR for air pollution, a second meeting will be held to integrate aerobiology and air pollution data in mobile technology and to propose ICPs for the prevention of severe exacerbations and asthma during peaks of allergens and/or pollution. This meeting will also consider the deployment to other chronic diseases (Fig. 4) and the impact of biodiversity in chronic diseases [98].

## Embedding next-generation care pathways in the EU and global political agendas for allergic and chronic respiratory diseases

The Polish Presidency of the EU Council (2011) targeted CRDs in children to promote their early recognition, prevention and management to ultimately impact active and healthy ageing (AHA) [99]. The developmental determinants of CRDs in ageing were reinforced during the Cyprus Presidency of the EU Council "Healthy ageing across the lifecycle" (2012) [100] and an EU-NIH meeting held in Montpellier (2013) [101].

The objective of AIRWAYS-ICPs [102] was to launch a collaboration to develop multi-sectoral ICPs for CRDs in European countries and regions. AIRWAYS-ICPs was initiated in 2014 by the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA, DG Santé and DG CONNECT) [103] as a GARD (Global Alliance against Chronic Respiratory Diseases) demonstration project [104]. In collaboration with GARD, the Directorate General of Health of Portugal, the EIP on AHA and the Région Occitanie (France), a high-level meeting was organized July 1, 2015 with all major European scientific societies and patient's organizations in Lisbon to review the implementation results of AIRWAYS ICPs [105].

Euforea (European Forum for Research and Education in Allergy and Airway Diseases) [56] proposed an annual stepwise strategy at the EU or ministerial levels. A European Symposium on Precision Medicine in Allergy and Airways Diseases was held at the EU Parliament October 14, 2015 [106]. Another EU Parliament meeting was held

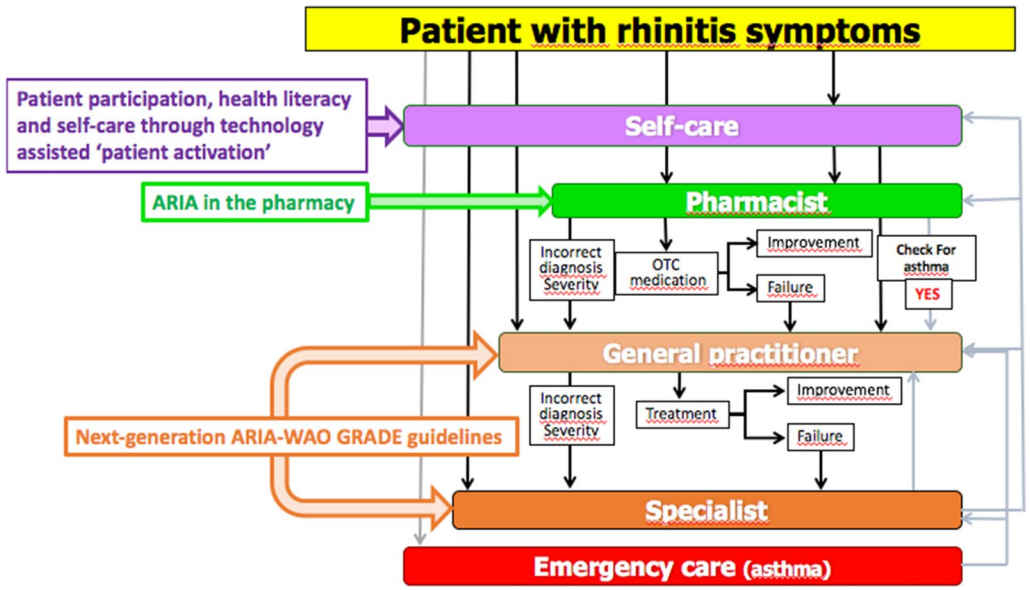


**Fig. 3** Next-generation ICPs for rhinitis and asthma multi-morbidity

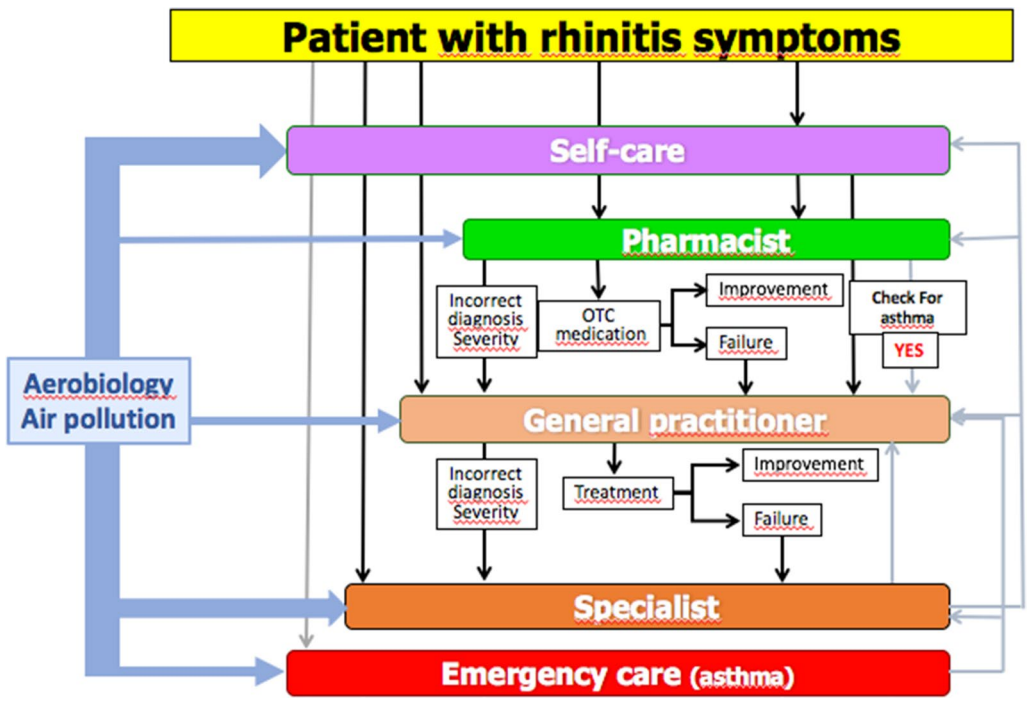


**Fig. 4** Embedding aerobiology and air pollution in ICPs

in Brussels March 29, 2017 on the Prevention and Self-Management of CRDs using novel mobile health tools [37, 56, 97].

POLLAR (Impact of air POLLution on Asthma and Rhinitis, EIT Health) is focusing on the impact of allergens and air pollution on airway diseases and aims to propose novel ICPs integrating pollution, sleep and patients' literacy and to assess the societal implications of the interaction [57].

Euforea organized an EU Summit in Vilnius, Lithuania (March 2018) in collaboration with the Ministers of Health of Lithuania, Moldova, Georgia and Ukraine. The aim was to discuss and start the implementation of the POLLAR concepts, and to deploy it to EU neighboring countries. The Vilnius Declaration on Chronic Respiratory Diseases proposed multisectoral ICPs embedding guided self-management, mHealth and air pollution in CRDs [107].

The joint meeting discussed in this report (December 3, 2018) proposed next-generation care pathways based on the Vilnius Declaration.

MASK has been selected by the European Commission's Directorate-General for Health and Food Safety (DG SANTE) and the newly-established Commission Expert Group "Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases" as a Good Practice (GP) in the field of digitally-enabled, integrated, person-centred care.

On May 3, 2019, a Euforea-led meeting took place in the Parliament of Malta to review the results of the December 3 meeting and to propose practical strategies at the EU and global levels with GARD.

This new next-generation care pathway is completely aligned with the recommendations issued by the Thematic Network SHAFE—Smart Healthy Age-Friendly Environments (approved by the European Commission—DG SANTE and DG CONNECT)—on its Joint Statement delivered 12th November 2018. The Statement underlined the need to patient empowerment and active involvement in its healthcare process and also urged the use of lifestyle medicine that provides effective impact on the patient's wellbeing.

## Conclusions

There is a need to support the digital transformation of health and care with integrated care. An innovative patient-centered approach is proposed by the ARIA expert group for rhinitis and asthma multimorbidity to be scaled up to chronic diseases.

## Additional file

**Additional file 1.** The MASK Study Group.

#### Abbreviations

AIRWAYS ICPs: integrated care pathways for airway diseases; AR: allergic rhinitis; ARIA: Allergic Rhinitis and its Impact on Asthma; BTS/SIGN: British Thoracic Society/Scottish Intercollegiate Guidelines Network; CRD: chronic respiratory diseases; EIP on AHA: European Innovation Partnership on Active and Healthy Ageing; EIT-Health: European Institute for Innovation and technology-Health; Euforea: European Forum for Research and Education in Allergy and Airway Diseases; GARD: Global Alliance against Chronic Respiratory Diseases; GDPR: General Data Privacy Regulation; GLASS-ARIA: Global Allergy Simple Solution; GP: general practitioner; GRADE: Grading of Recommendation, Assessment, Development and Evaluation; ICP: integrated care pathways; MASK: Mobile Airways Sentinel Network; MHealth: mobile health; OTC: over-the-counter; PG: pocket guides; POLLAR: Impact of Air POLLution in Asthma and Rhinitis; RWE: Real World Evidence; SDM: shared decision making; WAO : World Allergy Organization; WHO: World Health Organization.

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#### MASK Study group

See Additional file 1.

#### Authors' contributions

All authors are MASK members and have contributed to the design of the project. Many authors also included users and disseminated the project in their own country. Moreover, JB, HJ, AT, ME, TZ, IA, IJA, JMA, CB, SBA, IB, GB, EC, AAC, WC, WJF, JF, MI, LK, VK, LTT, DLL, DL, OML, EM, JM, YO, NP, NPT, HP, CR, BS, STS, IT, AV, AAM, MTV, SW, SW, XB, AB, SB, NB, GWC, VC, AMC, LC, AMCS, DC, EC, ME, GM, JM, EM, LM, GO, JLP, FP, DS, RvdK, AZ participated in the meeting held in Paris, December 3, 2018. All authors read and approved the final manuscript.

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All authors gave their agreement for the publication of the paper.

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Dr. Ansotegui reports personal fees from Mundipharma, Roxall, Sanofi, MSD, Faes Farma, Hikma, UCB, Astra Zeneca, outside the submitted work. Dr. Bosnic-Anticevich reports grants from TEVA, personal fees from TEVA, Boehringer Ingelheim, AstraZeneca, Sanofi, Mylan, outside the submitted work. Dr. Bousquet reports personal fees and others from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, others from Kyomed, outside the submitted work. Dr. Boulet reports and Disclosure of potential conflicts of interest—last 3 years. Research grants for participation to multicentre studies, AstraZeneca, Boston Scientific, GlaxoSmithKline, Hoffman La Roche, Novartis, Ono Pharma, Sanofi, Takeda. Support for research projects introduced by the investigator AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck, Takeda. Consulting and advisory boards Astra Zeneca, Novartis, Methapharm. Royalties Co-author of "Up-To-Date" (occupational asthma). Nonprofit grants for production of educational materials Astra-Zeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck Frosst, Novartis. Conference fees AstraZeneca, GlaxoSmithKline, Merck, Novartis. Support for participation in conferences and meetings Novartis, Takeda. Other participations Past president and Member of the Canadian Thoracic Society Respiratory Guidelines Committee; Chair of the Board of Directors of the Global Initiative for Asthma (GINA). Chair of Global Initiative for Asthma (GINA) Guidelines Dissemination and Implementation Committee; Laval University Chair on Knowledge Transfer, Prevention and Education in Respiratory and Cardiovascular Health; Member of scientific committees for the American College of Chest Physicians, American Thoracic Society, European Respiratory Society and the World Allergy Organization; 1st Vice-President of the Global Asthma Organization "InterAsma". Dr. Casale reports grants and non-financial support from Stallergenes, outside the submitted work. Dr. Cruz reports grants and personal fees from GlaxoSmithKline, personal fees from Boehrinher Ingelheim, AstraZeneca, Novartis, Merk, Sharp & Dohme, MEDA Pharma, EUROFARMA, Sanofi Aventis, outside the submitted work. Dr. Ebisawa reports personal fees from DBV

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